

## **REMARKS**

In response to the Office Action mailed February 2, 2009 and in further response to the Office Action mailed July 10, 2008, Claims 16-27 are pending and stand rejected. Claims 16, 23 and 25 have been amended. Claim 21 has been cancelled pursuant to the species restriction requirement of Claim 16 and consistent with species restriction election. Support for the amendments may be found generally throughout the specification and more specifically within paragraphs [0005], [0008-0009], [0031], [0029], [0033], [0037], Figure 1, Table 1 and the original claims inclusive.

### **Claim Rejections**

#### **I. 35 USC 112, First paragraph – Enablement**

Claims 16-27 stand rejected under 35, USC 1<sup>st</sup> paragraph for alleged lack of enablement. The Examiner acknowledges enablement for a method producing two specific polypeptides from two specific cell types, but alleges lack of enablement for a method for making any substance from any cell type. Applicants respectfully traverse and overcome this rejection.

Claim 16, as amended, is directed to a method of producing an immunoglobulin ( a specific type of polypeptide) from culturing CHO (Chinese Hamster Ovary) cells that produce said immunoglobulin in the presence of a nutrient media that results in a degree of glucose limitation (DGL). A specific cell type is thus specifically claimed, as well as is the substance produced by said method (see paragraphs 29-31 and 37 for support).

Applicants also respectfully note that one of ordinary skill in the art knows that the production of a recombinant polypeptide is dependent upon the kind of cell in which it is expressed. Thus, the cultivation medium and cultivation conditions therefore are optimized depending upon the identity of the cell in order to provide the best growth conditions for the cell.

Claim 16 identifies the cell as a CHO cell. Accordingly, a person of ordinary skill in the art would easily identify a culture medium and culture conditions suitable for said cell without undue burden, much less without undue experimentation. Applicants indeed recite in paragraph [0033] examples of glucose-containing media which can be used as the culture medium. One of ordinary skill in the art would understand from paragraph [0033] that as long as the glucose-containing medium chosen was not limiting with regard to other components, that the chosen glucose-containing media could be used in Applicants' claimed method (Claim 16).

With regard to the term DGL, Applicants respectfully note that this term is directed to a limitation of available glucose in the cultivation medium whereby the medium is not limiting in any other component ([005] "... in such a manner that glucose limitation occurs...", [008] "... it is important that there is no other limitation by other substrates..."). Therefore, the only parameter to be known is the specific glucose consumption rate of the cultivated CHO cell.

In other words, with respect to Claim 16, any glucose-containing medium can be used that is suitable for the growth of the respective CHO cell and only the glucose concentration of said medium has to be determined/adjusted. Therefore, any medium suitable for the cultivation of CHO cells is also suitable for the method according to the invention as only the glucose concentration has relevance with the proviso that all other components are not limiting. Such conditions can easily be determined by a person of skill in the art.

Accordingly, Applicants respectfully submit that Claim 16 as amended, and dependent claims thereon, are enabled. Applicants thus respectfully request that the 112, 1<sup>st</sup> paragraph rejection be withdrawn and claims 16-20 and 24-27 be placed into condition for allowance.

II. 35 USC 112, First paragraph – Written Description

Claims 16-27 stand rejected under 35, USC 1<sup>st</sup> paragraph for alleged lack of written description. Specifically, the Examiner contends that the specification provides an inadequate description of the nutrient media of Claim 16 such that a person of ordinary skill in the art could ascertain and practice the claimed method. Applicants respectfully traverse and overcome this rejection.

Claim 16, as amended, is directed to a method of producing an immunoglobulin (a specific type of polypeptide) from culturing CHO (Chinese Hamster Ovary) cells that produce said immunoglobulin in the presence of a glucose-containing media that results in a degree of glucose limitation (DGL). A specific cell type is thus specifically claimed, as well as is the substance produced by said method (see paragraphs 29-31 and 37 for support).

Applicants also respectfully note that one of ordinary skill in the art knows that the production of a recombinant polypeptide is dependent upon the kind of cell in which it is expressed. Thus, the cultivation medium and cultivation conditions therefore are optimized depending upon the identity of the cell in order to provide the best growth conditions for the cell.

Claim 16 identifies the cell as a CHO cell. Accordingly, a person of ordinary skill in the art would easily identify a glucose-containing culture medium and culture conditions suitable for said cell without undue burden, much less without undue experimentation. Applicants indeed recite in paragraph [0033] several examples of glucose-containing media which can be used as the culture medium. One of ordinary skill in the art would understand from paragraph [0033] that as long as the glucose-containing medium chosen was not limiting with regard to other components, that the chosen glucose-containing media could be used in Applicants' claimed method (Claim 16).

Accordingly, Applicants respectfully submit that *University of Rochester* is not analogous to Claim 16 as herein amended. In *Rochester*, the invention itself (the compounds which had a purported specific function) were not identified specifically and no examples of compounds having the claimed function were identified or even mentioned. In Claim 16, the invention is a method of producing an immunoglobulin from culturing CHO cells via the inventive step of measuring DGL in the cultivation medium. Specific examples of the cultivation media are given, both in the description and examples of the specification, so that one of ordinary skill in the art would understand the scope of the medium. The term media is thus defined by words (must be glucose-containing), examples (exemplified by several disclosures of specific glucose containing media), and function.

With regard to the term DGL, Applicants respectfully note that this term is directed to a limitation of available glucose in the cultivation medium whereby the medium is not limiting in any other component ([005] "... in such a manner that glucose limitation occurs...", [008] "... it is important that there is no other limitation by other substrates..."). Therefore, the only parameter to be known is the specific glucose consumption rate of the cultivated CHO cell.

In other words, with respect to Claim 16, any glucose-containing medium can be used that is suitable for the growth of the respective CHO cell and only the glucose concentration of said medium has to be determined/adjusted. Therefore, any glucose-containing medium suitable for the cultivation of CHO cells is also suitable for the method according to the invention as only the glucose concentration has relevance with the proviso that all other components are not limiting. Given this disclosure, and the additional disclosure of specific examples of such glucose-containing media, Applicants respectfully submit that one of ordinary skill in the art could and would be able to choose a nutrient media to practice Applicants' claimed invention.

Accordingly, Applicants respectfully submit that Claim 16 as amended, and dependent claims thereon, are adequately described. Applicants thus respectfully request that the 112, 1<sup>st</sup> paragraph rejection be withdrawn and claims 16-20 and 24-27 be placed into condition for allowance.

III. 35 USC 112, Second paragraph – Definiteness

Claims 16-27 also stand rejected under 35, USC 2<sup>nd</sup> paragraph for alleged indefiniteness. Applicants respectfully traverse and overcome this rejection.

1. The Examiner contends Claim 16 is indefinite for a) omitting a recovery step, and for the terms: b) nutrient media, c) DGL (the DGL maintenance, DGL consumption rate) and d) consumption rate. Applicants respectfully traverse and overcome this rejection.

a) Applicants have amended Claim 16 to recite a recovery step of the immunoglobulin. Accordingly, Applicants respectfully submit that the 112, 2<sup>nd</sup> paragraph rejection to claim 16 in this regard is obviated and should be withdrawn.

Applicants hereby reiterate the arguments above with regard to the definition of nutrient glucose-containing media. The glucose-containing media is defined so that one of ordinary skill in the art would comprehend its meaning. Accordingly, Applicants respectfully submit that the 112, 2<sup>nd</sup> paragraph rejection to claim 16 in this regard is obviated and should be withdrawn.

b) Applicants also hereby reiterate the arguments above with regard to the term DGL. this term is directed to a limitation of available glucose in the cultivation medium whereby the medium is not limiting in any other component ([005] "... in such a manner that glucose limitation occurs...", [008] "... it is important that there is no other limitation by other substrates..."). Therefore, the only parameter to be known is the specific glucose consumption rate of the cultivated CHO cell.

DGL maintenance thus means, as outlined in [009], how the available glucose is used, specifically the term "maintenance" denotes that "glucose is mainly used [...] for the product [production] and less for cell growth".

DGL consumption rate is similarly described and defined. The term "maximum known for specific consumption rate" as used in claim 16 is directed to the maximum consumption rate observed with the CHO cell used in the method according to the invention. This rate will not be changed due to future findings as this rate does not depend on the cultivation method, such as fed-batch, continuous, or high cell fermentation, but on the cell type. As the cell type is given in the amended claim (CHO cell) a person skilled in the art at one knows the value related to the term "maximum specific glucose consumption rate" of a CHO cell. The term as used in the claim is thus defined/limited to the specific cell type (CHO). Therefore, the term "maximum specific glucose consumption rate of a CHO cell", i.e., the maximum glucose consumption rate per single CHO cell known, is a fixed value and likewise the "currently observed specific consumption rate" is also clear to a person of skill in the art as it has to be between zero and the maximum specific consumption rate.

Thus, Applicants respectfully submit that the 112, 2<sup>nd</sup> paragraph rejection to claim 16 in this regard is obviated and should be withdrawn.

c) Applicants have amended claim 16 to clarify what (glucose) is being consumed. Accordingly, Applicants respectfully submit that the 112, 2<sup>nd</sup> paragraph rejection to claim 16 in this regard is obviated and should be withdrawn.

2. The Examiner contends Claims 19-20 are indefinite for the term "maximum expected cell count". Applicants respectfully traverse and overcome this rejection.

Applicants respectfully note that the term "maximum expected cell count" is directed to the maximum cell density that can be obtained by culturing a CHO cell. For example see figure 1 and Table 1, in which a maximum cell density of  $2.08 \times 10^7$  cells/ml is listed. Accordingly, Applicants respectfully submit that the 112, 2<sup>nd</sup> paragraph rejection to claims 19-20 in this regard is obviated and should be withdrawn.

3. The Examiner contends Claims 19-20 are also indefinite for the amount of glucose to be consumed by the cells. Applicants respectfully traverse and overcome this rejection.

Applicants respectfully note the amount of glucose to be consumed depends on the cell density in the cultivation and as such cannot be specified in absolute terms by giving a defined number. However, as mentioned above, the term "maximum specific glucose consumption rate of a CHO cell", i.e., the maximum glucose consumption rate per single CHO cell known, is a fixed value. Claims 19-20 reflect a limitation on this rate.

Accordingly, Applicants respectfully submit that the 112, 2<sup>nd</sup> paragraph rejection to claims 19-20 in this regard is obviated and should be withdrawn.

4. Claim 21 has been cancelled due to the amendment of Claim 16 consistent with the species restriction requirement. Claim 23 has been amended to define the abbreviations for EPO and PA and to properly depend upon Claim 16.

Accordingly, Applicants respectfully submit that the 112, 2<sup>nd</sup> paragraph rejection to claims 21 and 23 in this regard is obviated and should be withdrawn.

5. The Examiner seeks clarification for the Claim 24 term "before glucose limitation occurs" as it relates to Claim 16. Applicants respectfully traverse and overcome this rejection.

Applicants note that the term "before glucose limitation occurs" in claim 24 is directed to the beginning of the cultivation. Accordingly, Applicants respectfully submit that the rejection to claim 24 has been overcome.

6. Applicants have amended Claim 25 to delete the alleged indefinite term. Accordingly, Applicants respectfully submit that the indefinite rejection to Claim 25 has been rendered moot.

No further fee is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

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